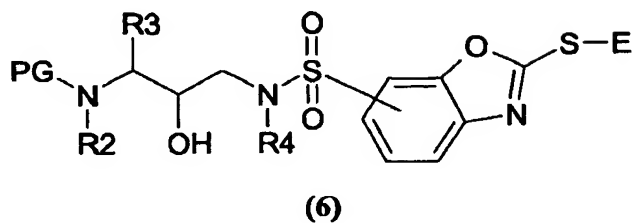


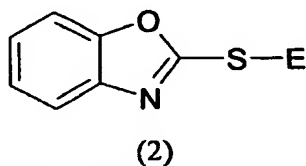
-53-

CLAIMS

1. A method for preparing a compound of formula (6),

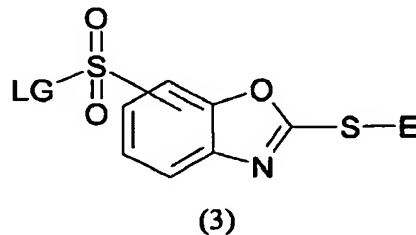


and salts, stereoisomeric forms, and racemic mixtures thereof, characterized in that said method starts from a compound of formula (2),



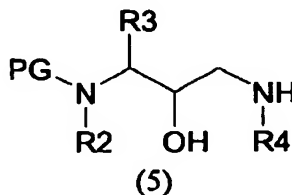
wherein E is an electrophilic moiety;

transforming compound of formula (2) into a compound of formula (3),



wherein LG is a leaving group; and

reacting compound of formula (3) with a compound of formula (5),



wherein

PG is a protecting group;

R₂ is hydrogen or C₁₋₆alkyl;

25 R₃ is C₃₋₇cycloalkyl, aryl, Het¹, Het², or C₁₋₆alkyl optionally substituted with C₃₋₇cycloalkyl, aryl, Het¹, or Het²; wherein each C₃₋₇cycloalkyl, aryl, Het¹, and Het² may be optionally substituted with one or more groups selected from oxo, C₁₋₆alkyloxy, C₁₋₆alkyl,

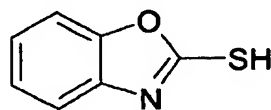
-54-

C₁₋₆alkylsulfonyl, aminosulfonyl, amino, C₁₋₆alkylcarbonylamino, hydroxyC₁₋₆alkyl, cyano, C₁₋₆alkyloxycarbonyl, aminocarbonyl, halogen or trifluoromethyl, wherein each amino maybe mono- or disubstituted with C₁₋₆alkyl;

- R₄** is selected from the group comprising hydrogen, C₁₋₄alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C₁₋₄alkyl)aminocarbonyl, C₃₋₇cycloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, or C₁₋₆alkyl optionally substituted with one or more substituents each independently selected from aryl, Het¹, Het², C₃₋₇cycloalkyl, C₁₋₄alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C₁₋₄alkyl)aminocarbonyl, aminosulfonyl, C₁₋₄alkyl-S(=O)_t, hydroxy, cyano, halogen and amino optionally mono- or disubstituted where the substituents are each independently selected from C₁₋₄alkyl, aryl, arylC₁₋₄alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₄alkyl, Het¹, Het², Het¹C₁₋₄alkyl and Het²C₁₋₄alkyl; and

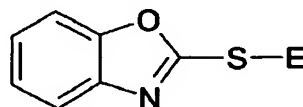
t is zero, one or two.

2. A method according to claim 1 for preparing a compound of formula (6), characterized in that said method comprises the steps of:
alkylating a compound of formula (1)



(1)

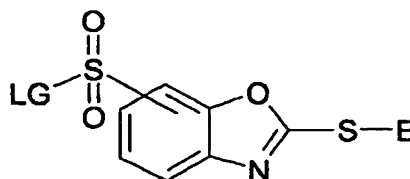
resulting into a compound of formula (2);



(2)

wherein **E** is a C₁₋₆alkyl;

reacting compound of formula (2) with a sulfonation agent, resulting in a compound of formula (3);

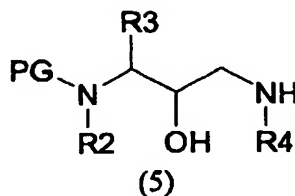


(3)

wherein **LG** is a leaving group; and

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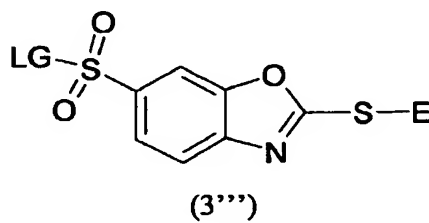
coupling compound of formula (3) with a compound of formula (5).



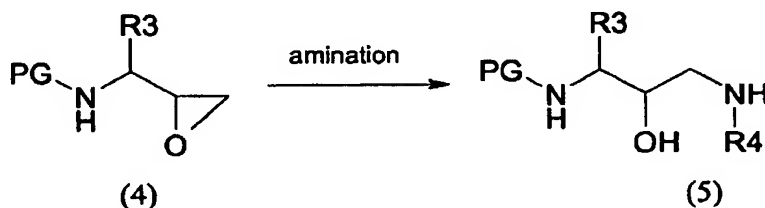
5

wherein PG is a protecting group; and
wherein R_2 , R_3 , and R_4 are as claimed in claim 1.

3. A method according to any one of claims 1 to 2, characterized in that compound of
10 formula (3) is a compound of formula (3''').

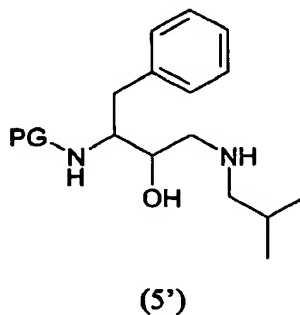


- 15 4. A method according to any one of claims 1 to 3, characterized in that compound of
formula (5) is obtained by amination of an epoxide-containing compound of formula
(4), and the amination reagent is H_2N-R_4 , wherein R_4 is as claimed in any one of claims
1 to 3.



20

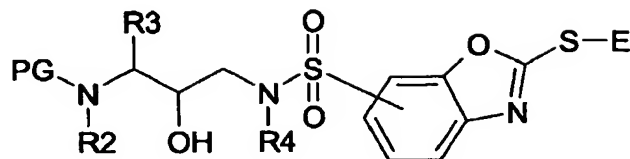
5. A method according to any one of claims 1 to 4, wherein compound of formula (5) is
compound of formula (5').



25

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6. A compound having formula (6)



(6)

and salts, stereoisomeric forms, and racemic mixtures thereof, characterized in that PG, R₂, R₃, R₄, and E are as defined in any one of claims 1 to 5.

7. A compound according to claim 6, characterized in that

R₂ is hydrogen;

R₃ is arylC₁₋₄alkyl, arylmethyl, or phenylmethyl;

R₄ is unsubstituted C₁₋₆alkyl or C₁₋₆alkyl substituted with one or more substituents selected from aryl, Het¹, Het², C₃₋₇cycloalkyl and amino optionally mono- or disubstituted where the substituents are selected from C₁₋₄alkyl, aryl, Het¹ and Het².

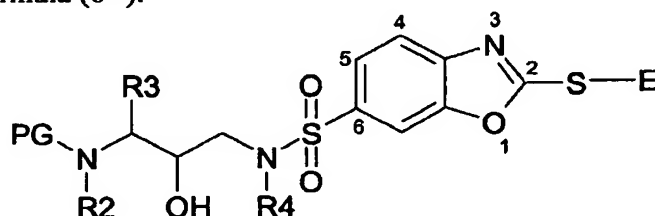
8. A compound according to any one of claims 6 to 7, characterized in that

R₂ is hydrogen;

R₃ is phenylmethyl; and

R₄ is isobutyl.

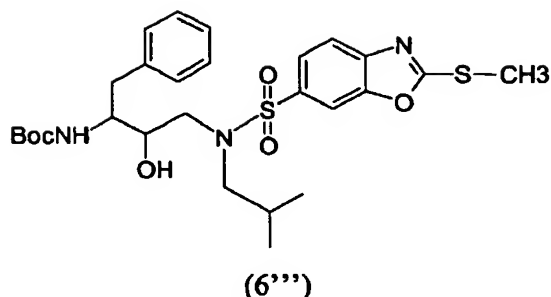
9. A compound according to any one of claims 6 to 8, characterized in that the compound has formula (6'').



(6'')

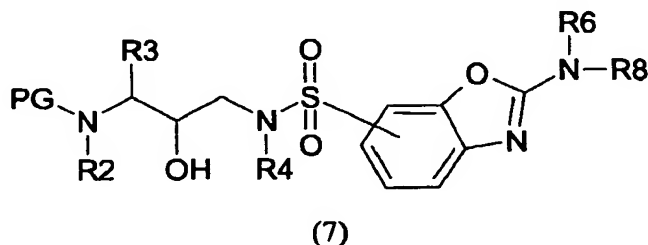
10. A compound according to any one of claims 6 to 9, characterized in that the compound has formula (6''').

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11. A compound according to any one of claims 6 to 10, characterized in that said
 5 compound is in the form of a salt selected from trifluoroacetate, fumarate, chloroacetate
 and methanesulfonate.

12. A method for preparing a compound of formula (9), wherein said method comprises
 the methods according to any one of claims 1 to 5, characterised in that said method
 10 further comprises
 aminating compound of formula (6) to obtain compound of formula (7), wherein



15

R_6 is hydrogen, hydroxy, C_{1-6} alkyl, $Het^1 C_{1-6}$ alkyl, $Het^2 C_{1-6}$ alkyl, amino C_{1-6} alkyl
 whereby the amino group may optionally be mono- or di-substituted with C_{1-4} alkyl;

R_8 is hydrogen, C_{1-6} alkyl, or $-A-R_7$;

A is C_{1-6} alkanediyl, $-C(=O)-$, $-C(=S)-$, $-S(=O)_2-$, C_{1-6} alkanediyl- $C(=O)-$,
 20 C_{1-6} alkanediyl- $C(=S)-$ or C_{1-6} alkanediyl- $S(=O)_2-$; whereby the point of attachment to
 the nitrogen atom is the C_{1-6} alkanediyl group in those moieties containing said group;

R_7 is C_{1-6} alkyloxy, Het^1 , Het^1oxy , Het^2 , Het^2oxy , aryl, aryloxy, C_{3-7} cycloalkyl,
 or optionally mono- or disubstituted amino; and

in case $-A-$ is other than C_{1-6} alkanediyl then R_7 may also be C_{1-6} alkyl,
 25 $Het^1 C_{1-4}$ alkyl, $Het^1oxy C_{1-4}$ alkyl, $Het^2 C_{1-4}$ alkyl, $Het^2oxy C_{1-4}$ alkyl, aryl C_{1-4} alkyl,
 aryloxy C_{1-4} alkyl or amino- C_{1-6} alkyl; whereby each of the amino groups in the
 definition of R_7 may optionally be substituted with one or more substituents selected
 from C_{1-4} alkyl, C_{1-4} alkylcarbonyl, C_{1-4} alkyloxycarbonyl, aryl, arylcarbonyl,
 aryloxycarbonyl, Het^1 , Het^2 , aryl C_{1-4} alkyl, Het^1-C_{1-4} alkyl or $Het^2 C_{1-4}$ alkyl; and

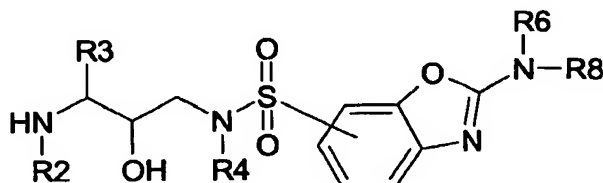
30 $-A-R_7$ may also be hydroxy C_{1-6} alkyl; and

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R_6 and $-A-R_7$ taken together with the nitrogen atom to which they are attached may also form Het^1 or Het^2 ;

deprotecting compound of formula (7) to obtain compound of formula (8),

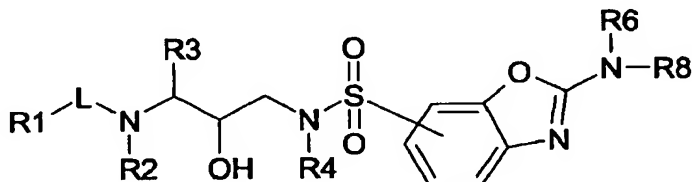
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(8)

coupling a radical of formula R_1-L- to obtain compound of formula (9),

10

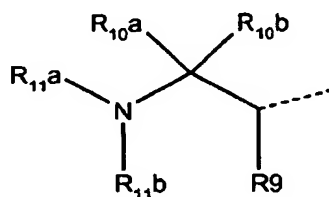


(9)

and N -oxides, salts, stereoisomeric forms, racemic mixtures, prodrugs, esters and metabolites thereof, wherein

R_1 is selected from the group comprising hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, aryl C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-6} alkyl, aryl, Het^1 , Het^1C_{1-6} alkyl, Het^2 , Het^2C_{1-6} alkyl; and R_1 may also be a radical of formula (10)

15



(10)

20

R_9 , R_{10a} and R_{10b} are, each independently, hydrogen, C_{1-4} alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C_{1-4} alkyl)aminocarbonyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl or C_{1-4} alkyl optionally substituted with aryl, Het^1 , Het^2 , C_{3-7} cycloalkyl, C_{1-4} alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C_{1-4} alkyl)-aminocarbonyl, aminosulfonyl, C_{1-4} alkyl $S(O)_t$, hydroxy, cyano, halogen or amino optionally mono- or disubstituted where the substituents are each independently selected from C_{1-4} alkyl, aryl, aryl C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-4} alkyl, Het^1 , Het^2 , Het^1C_{1-4} alkyl and

25

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Het²C₁₋₄alkyl; whereby R₉, R_{10a} and the carbon atoms to which they are attached may also form a C₃₋₇cycloalkyl radical;

when L is -O-C₁₋₆alkanediyl-C(=O)- or -NR₁₂-C₁₋₆alkanediyl-C(=O)-, then R₉ may also be oxo;

- 5 R_{11a} is selected from the group comprising hydrogen, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, aryl, aminocarbonyl optionally mono- or disubstituted, aminoC₁₋₄alkylcarbonyloxy optionally mono- or disubstituted, C₁₋₄alkyloxycarbonyl, aryloxycarbonyl, Het¹oxycarbonyl, Het²oxycarbonyl, aryloxycarbonylC₁₋₄alkyl, arylC₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyl, C₃₋₇cycloalkylcarbonyl, C₃₋₇cycloalkyl-
 10 C₁₋₄alkyloxycarbonyl, C₃₋₇cycloalkylcarbonyloxy, carboxylC₁₋₄alkylcarbonyloxy, C₁₋₄alkylcarbonyloxy, arylC₁₋₄alkylcarbonyloxy, arylcarbonyloxy, aryloxycarbonyloxy, Het¹carbonyl, Het¹carbonyloxy, Het¹C₁₋₄alkyloxycarbonyl, Het²carbonyloxy, Het²C₁₋₄alkylcarbonyloxy, Het²C₁₋₄alkyloxycarbonyloxy or C₁₋₄alkyl optionally substituted with aryl, aryloxy, Het² or hydroxy; wherein the substituents on the amino
 15 groups are each independently selected from C₁₋₄alkyl, aryl, arylC₁₋₄alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkyl C₁₋₄alkyl, Het¹, Het², Het¹C₁₋₄alkyl and Het²C₁₋₄alkyl;

- R_{11b} is selected from the group comprising hydrogen, C₃₋₇cycloalkyl, C₂₋₆alkenyl,
 20 C₂₋₆alkynyl, aryl, Het¹, Het² or C₁₋₄alkyl optionally substituted with halogen, hydroxy, C₁₋₄alkylS(=O)_t, aryl, C₃₋₇cycloalkyl, Het¹, Het², amino optionally mono- or disubstituted where the substituents are each independently selected from C₁₋₄alkyl, aryl, arylC₁₋₄alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₄alkyl, Het¹, Het², Het¹C₁₋₄alkyl and Het²C₁₋₄alkyl;

- 25 whereby R_{11b} may be linked to the remainder of the molecule via a sulfonyl group; and

- L is selected from the group comprising -C(=O)-, -O-C(=O)-, -NR₁₂-C(=O)-, -O-C₁₋₆alkanediyl-C(=O)-, -NR₁₂-C₁₋₆alkanediyl-C(=O)-, -S(=O)₂-, -O-S(=O)₂-, -NR₁₂-S(=O)₂ whereby either the C(=O) group or the S(=O)₂ group is attached to the
 30 NR₂ moiety; whereby the C₁₋₆alkanediyl moiety is optionally substituted with a substituent selected from hydroxy, aryl, Het¹, and Het²;

R₁₂ is hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, arylC₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₆alkyl, aryl, Het¹, Het¹C₁₋₆alkyl, Het², Het²C₁₋₆alkyl;

R₂ is hydrogen or C₁₋₆alkyl;

- 35 R₃ is C₃₋₇cycloalkyl, aryl, Het¹, Het², or C₁₋₆alkyl optionally substituted with C₃₋₇cycloalkyl, aryl, Het¹, or Het²; wherein each C₃₋₇cycloalkyl, aryl, Het¹, and Het² may be optionally substituted with one or more groups selected from oxo, C₁₋₆alkyloxy, C₁₋₆alkyl,

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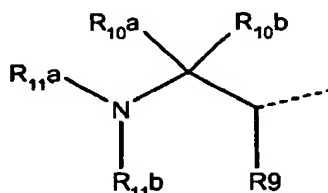
C₁₋₆alkylsulfonyl, aminosulfonyl, amino, C₁₋₆alkylcarbonylamino, hydroxyC₁₋₆alkyl, cyano, C₁₋₆alkyloxycarbonyl, aminocarbonyl, halogen or trifluoromethyl, wherein each amino maybe mono- or disubstitued with C₁₋₆alkyl;

- R₄** is selected from the group comprising hydrogen, C₁₋₄alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C₁₋₄alkyl)aminocarbonyl, C₃₋₇cycloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, or C₁₋₆alkyl optionally substituted with one or more substituents each independently selected from aryl, Het¹, Het², C₃₋₇cycloalkyl, C₁₋₄alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C₁₋₄alkyl)aminocarbonyl, aminosulfonyl, C₁₋₄alkyl-S(=O)_t, hydroxy, cyano, halogen and amino optionally mono- or disubstitued where the substituents are each independently selected from C₁₋₄alkyl, aryl, arylC₁₋₄alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₄alkyl, Het¹, Het², Het¹C₁₋₄alkyl and Het²C₁₋₄alkyl; and

t is zero, one or two.

13. The method according to claim 12, wherein

R₁ is a radical of formula (10)



(10)

20

- R₉, R_{10a} and R_{10b}** are, each independently, hydrogen, C₁₋₄alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C₁₋₄alkyl)aminocarbonyl, C₃₋₇cycloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl or C₁₋₄alkyl optionally substituted with aryl, Het¹, Het², C₃₋₇cycloalkyl, C₁₋₄alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C₁₋₄alkyl)-aminocarbonyl, aminosulfonyl, C₁₋₄alkylS(O)_t, hydroxy, cyano, halogen or amino optionally mono- or disubstitued where the substituents are each independently selected from C₁₋₄alkyl, aryl, arylC₁₋₄alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkyl-C₁₋₄alkyl, Het¹, Het², Het¹C₁₋₄alkyl and Het²C₁₋₄alkyl;

- whereby **R₉, R_{10a}** and the carbon atoms to which they are attached may also form a C₃₋₇cycloalkyl radical;

- R_{11b}** is hydrogen, C₃₋₇cycloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, aryl, Het¹, Het² or C₁₋₄alkyl optionally substituted with halogen, hydroxy, C₁₋₄alkylS(=O)_t, aryl, C₃₋₇cycloalkyl, Het¹, Het², amino optionally mono- or disubstitued where the

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substituents are each independently selected from C_{1-4} alkyl, aryl, aryl C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-4} alkyl, Het¹, Het², Het¹ C_{1-4} alkyl and Het² C_{1-4} alkyl; whereby R_{11b} may be linked to the remainder of the molecule via a sulfonyl group;

5 t is zero, one or two;

L is $-C(=O)-$, $-O-C(=O)-$, $-NR_{12}-C(=O)-$, $-O-C_{1-6}$ alkanediyl- $C(=O)-$, $-NR_{12}-C_{1-6}$ alkanediyl- $C(=O)-$, $-S(=O)_2-$, $-O-S(=O)_2-$, $-NR_{12}-S(=O)_2$ whereby either the $C(=O)$ group or the $S(=O)_2$ group is attached to the NR_2 moiety; whereby the C_{1-6} alkanediyl moiety is optionally substituted with a substituent selected from
10 hydroxy, aryl, Het¹, and Het²;

R_{12} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, aryl C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-6} alkyl, aryl, Het¹, Het¹ C_{1-6} alkyl, Het², Het² C_{1-6} alkyl; and

R_4 is hydrogen, C_{1-4} alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C_{1-4} alkyl)aminocarbonyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl
15 optionally substituted with one or more substituents selected from aryl, Het¹, Het², C_{3-7} cycloalkyl, C_{1-4} alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C_{1-4} alkyl)-aminocarbonyl, aminosulfonyl, C_{1-4} alkyl $S(=O)_t$, hydroxy, cyano, halogen and amino optionally mono- or disubstituted where the substituents are selected from C_{1-4} alkyl, aryl, aryl C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl- C_{1-4} alkyl, Het¹, Het², Het¹ C_{1-4} alkyl
20 and Het² C_{1-4} alkyl.

14. The method according to any one of claims 12 to 13, wherein one or more of the following restrictions apply:

R_1 is hydrogen, Het¹, Het², aryl, Het¹ C_{1-6} alkyl, Het² C_{1-6} alkyl, aryl C_{1-6} alkyl,
25 more in particular, R_1 is a saturated or partially unsaturated monocyclic or bicyclic heterocycle having 5 to 8 ring members, which contains one or more heteroatom ring members selected from nitrogen, oxygen or sulfur and which is optionally substituted, or phenyl optionally substituted with one or more substituents;

R_2 is hydrogen;

30 L is $-C(=O)-$, $-O-C(=O)-$, $-O-C_{1-6}$ alkanediyl- $C(=O)-$, more in particular, L is $-O-C(=O)-$ or $-O-C_{1-6}$ alkanediyl- $C(=O)-$, whereby in each case the $C(=O)$ group is attached to the NR_2 moiety;

R_3 is aryl C_{1-4} alkyl, in particular, arylmethyl, more in particular phenylmethyl;

R_4 is optionally substituted C_{1-6} alkyl, in particular unsubstituted C_{1-6} alkyl or
35 C_{1-6} alkyl optionally substituted with one or more substituents selected from aryl, Het¹, Het², C_{3-7} cycloalkyl and amino optionally mono- or disubstituted where the substituents are selected from C_{1-4} alkyl, aryl, Het¹ and Het²;

R_6 is hydrogen or methyl; and

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R_8 is hydrogen or methyl.

15. The method according to any one of claims 12 to 14, wherein

R_1-L is $Het^1-O-C(=O)$, $Het^2-C_{1-6}alkanediy-O-C(=O)$, aryl- $O-C_{1-6}alkanediy-$
 5 $C(=O)$ or aryl- $C(=O)$.

16. The method according to any one of claims 12 to 15, wherein

NR_6R_8 is amino, monomethylamino or dimethylamino.

10 17. The method according to any one of claims 12 to 16, wherein

R_1 is a Het^1 , or a $Het^1C_{1-6}alkyl$, and

L is $-O-C(=O)-$;

R_2 is hydrogen;

R_3 is phenylmethyl;

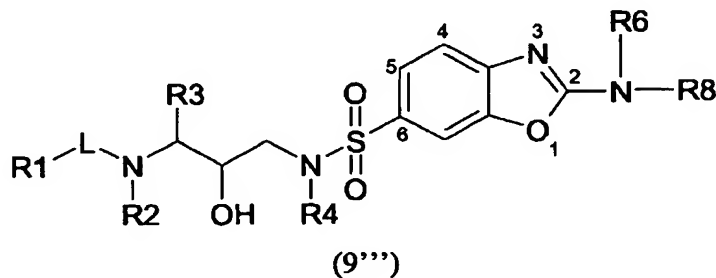
15 R_4 is isobutyl;

R_6 is hydrogen; and

R_8 is hydrogen or methyl.

18. The method according to any one of claims 12 to 17, wherein compound (9) has

20 formula (9''').



19. The method according to any one of claims 12 to 18, characterized in that
 25 compound of formula (9) is in the form of a salt selected from trifluoroacetate, fumarate, chloroacetate and methanesulfonate.

20. Use of a compound as claimed in any of claims 7 to 11 as an intermediate for preparing a retrovirus protease inhibitor of formula (9).